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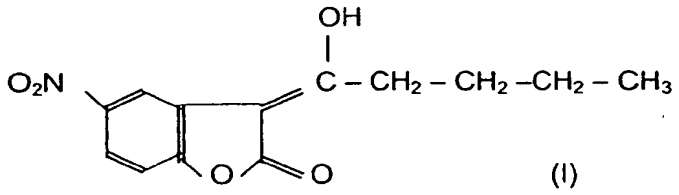
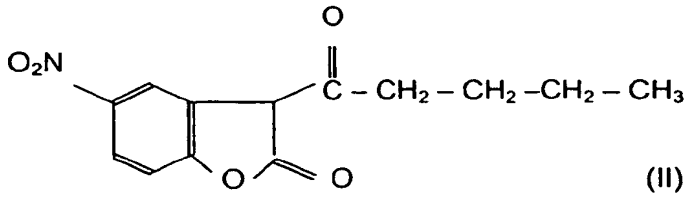
(54) 3-(1-Hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one, a process for the preparation thereof and the use thereof

(57) A compound corresponding to formula (I) or its ketonic tautomer form (II)



(I)



(II)

which is 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one, a process for the preparation and use of the compound corresponding to formula (I) or its tautomeric form (II), a process for the preparation and use, particularly for the production of synthesis intermediates.

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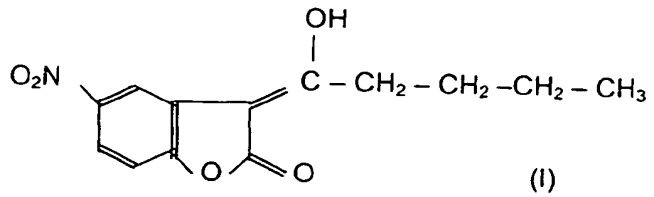
Description

[0001] The present invention relates to 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one and to its ketonic tautomer form 3-(1-oxo-pentyl)-5-nitro-3H-benzofuran-2-one.

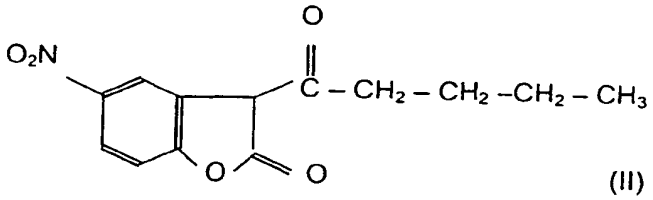
[0002] 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one is a new compound which may be used as a synthesis intermediate. In particular, it may be converted to 2-butyl-5-nitrobenzofuran by hydrolysis, decarboxylation and cyclisation, by simple heating in an acid medium. 2-butyl-5-nitrobenzofuran may act as an intermediate in the synthesis of an antiarrythmic, dronedarone.

[0003] The present invention provides, therefore, 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one corresponding to formula (I)



(I)

and its ketonic tautomer form, 3-(1-oxo-pentyl)-5-nitro-3H-benzofuran-2-one corresponding to formula (II)



(II)

[0004] The present invention also provides a process for the preparation of the compound corresponding to formula (I) and its ketonic tautomer form (II).

[0005] Finally, the present invention provides the use of the compound corresponding to formula (I) or its ketonic tautomer form (II) as a synthesis intermediate, particularly for the preparation of active pharmaceutical principles. In particular, the present invention provides the compound corresponding to formula (I) and the preparation thereof.

[0006] This preparation is characterised in that 5-nitro-3H-benzofuran-2-one is reacted, at a temperature above 30°C, with pentanoic anhydride and a salt of pentanoic acid, optionally in the presence of pentanoic acid, then the resulting reaction mixture is acidified, and then the expected product is isolated.

This method of operating constitutes an improvement to the process described by J.N. Chatterjea, J. Indian Chem. Soc. Vol. 33 no. 3, 1956, p. 175-182 and J. Indian Chem. Soc. Vol. 34, no.4, 1957, p. 299-305.

This improvement to the process relates to the acidification of the reaction mixture at the end of the reaction which allows better isolation of the expected product. A second improvement relates to the reduction in the amount of acid anhydride required for the reaction.

[0007] Under preferential conditions for carrying out the process according to the invention, 1 mole of 5-nitro-3H-benzofuran-2-one is reacted with 1 to 5 moles of pentanoic anhydride, 0.1 to 2 moles of a salt of pentanoic acid, and 0 to 1.5 moles of pentanoic acid, then the resulting reaction mixture is acidified, and then the expected product is isolated, if desired.

[0008] Under other preferential conditions for carrying out the process according to the invention, one mole of 5-nitro-3H-benzofuran-2-one is reacted with two moles of pentanoic anhydride and one mole of a salt of pentanoic acid, then the resulting reaction mixture is acidified, then the expected product is isolated.

[0009] In the implementation of the process according to the invention, the salt of pentanoic acid may be a salt of sodium, potassium or of tertiary amine. This salt may be prepared extemporaneously, preferably in situ, from pentanoic acid and a base. The base may be sodium carbonate.

[0010] In the implementation of the process according to the invention, the resulting reaction mixture is brought into contact with an acid. This acid will be preferably dilute sulfuric acid; indeed, it permits better recovery of the expected final product.

Still under preferential conditions for carrying out the process, the crude product obtained may be recrystallised in an acid. This acid will be advantageously acetic acid.

[0011] The present invention also provides the use of the product corresponding to formula (I) or its tautomeric form (II) for the production of synthesis intermediates. In particular, it provides the production of 2-butyl-5-nitro-benzofuran-2-one which may act as an intermediate in the synthesis of an antiarrhythmic agent, dronedarone.

[0012] The examples below will permit a better understanding of the invention.

EXAMPLE 1

[0013] The following are charged to a three-necked flask:

- 478.7 g (2.57 moles) of pentanoic anhydride
- 131.3 g (1.285 moles) of pentanoic acid
- 81.6 g (0.771 mole) of sodium carbonate
- 230 g (1.285 moles) of 5-nitro-3H-benzofuran-2-one

and the mixture is raised to a temperature of 80°C for a period of 6 hours, with stirring.
The mixture is cooled to 20°C and the following are added gradually within 15 minutes:

- 377.8 g (0.771 mole) of sulfuric acid diluted to 20%.

The temperature of the mixture rises to about 40°C.
The suspension is then cooled to 20°C and the precipitate is filtered. It is washed with 250 ml of deionised water then with 250 ml of heptane.
After oven drying under reduced pressure at 60°C, a crude product with a purity of 95% is obtained.
Pure 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one is obtained by recrystallisation in acetic acid.

[0014] The analysis of the product is as follows:

Melting point	164°C (DSC)
Elemental analysis (theoretical)	C 59.1% (59.3%), H 5.0% (4.9%), N 5.4% (5.3%)
NMR (H)	200 MHz
Solvent	DMSO

δ = 0.90 ppm	Triplet	J = 7.1 Hz	3H
δ = 1.37 ppm	Multiplet		2H
δ = 1.60 ppm	Multiplet		2H
δ = 2.94 ppm	Triplet	J = 7.9 Hz	2H
δ = 7.30 ppm	Doublet	J_{H7-H6} = 8.9 Hz	1H
δ = 8.05 ppm	Quadruplet	J_{H6-H7} = 8.9 Hz; J_{H6-H4} = 2.3 Hz	1H
δ = 8.38 ppm	Doublet	J_{H4-H6} = 2.3 Hz	1H

EXAMPLE 2

[0015] The following are charged to a three-necked flask:

- 96 g (1.6 moles) of 100% acetic acid
- 49 g (0.2 mole) of 40% sulfuric acid
- 26.3 g (0.1 mole) of 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one.

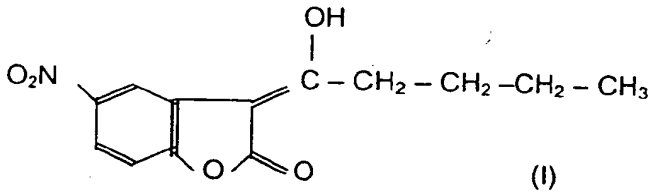
The mixture is brought to reflux, with stirring, over a period of 8 hours, the internal temperature being in the vicinity of 116°C.
An orange-coloured solution is gradually obtained with the liberation of gas.
The solution is cooled to ambient temperature and 50 g of water are added, then the solution is extracted twice under hot conditions with 140 g of heptane.

The combined organic phases are treated with 250 g of water and the pH is adjusted to 8 by adding a 30% potash solution (about 20 ml), then the aqueous phase is drawn off.
The separated organic phase is then dried by azeotropic distillation of water then the solvent is removed by distillation and the resulting oil is heated under reduced pressure in order to remove the traces of solvent.
A slightly yellow oil which crystallises at ambient temperature is thus obtained.
The 2-butyl-5-nitrobenzofuran obtained has a purity (high pressure liquid chromatography by external standardisation with respect to a reference standard) greater than 98% and a residual amount of heptane, by vapour phase chromatography, of less than 1.5%.
The NMR (H) spectrum 200 MHz (solvent: DMSO) is as follows:

δ = 0.90 ppm	Triplet	J = 7.2 Hz	3H
δ = 1.35 ppm	Multiplet		2H
δ = 1.66 ppm	Multiplet		2H
δ = 2.80 ppm	Triplet	J = 7.4 Hz	2H
δ = 6.80 ppm	Singlet		1H
δ = 7.70 ppm	Doublet	J_{H7H6} =9 Hz	1H
δ = 8.11 ppm	Doublet of Doublet	J_{H6H7} =9 Hz; J_{H6H4} = 2.3 Hz	1H
δ = 8.47 ppm	Doublet	J_{H4H6} = 2.3 Hz	1H

Claims

1. 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one, corresponding to formula (I), and 3-(1-oxopentyl)-5-nitro-3H-benzofuran-2-one, its ketonic tautomer form, corresponding to formula (II)



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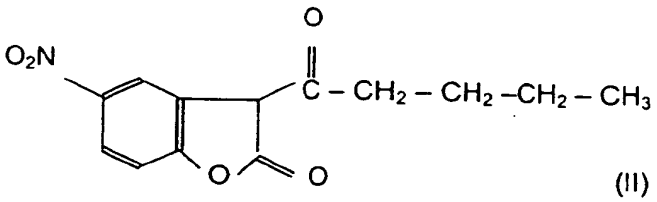

(II)

2. A process for the preparation of the two compounds of claim 1, characterised in that 5-nitro-3H-benzofuran-2-one is reacted, at a temperature above 30°C, with pentanoic anhydride and a salt of pentanoic acid, optionally in the presence of pentanoic acid, then the resulting reaction mixture is acidified, and then the expected product is isolated.

3. A process according to claim 2, characterised in that 1 mole of 5-nitro-3H-benzofuran-2-one is reacted with 1 to 5 moles of pentanoic anhydride, 0.1 to 2 moles of a salt of pentanoic acid and 0 to 1.5 moles of pentanoic acid, then the resulting reaction mixture is acidified and then the expected product is isolated.

4. A process according to claim 2 or 3, characterised in that 1 mole of 5-nitro-3H-benzofuran-2-one is reacted with

2 moles of pentanoic anhydride and 1 mole of a salt of pentanoic acid, then the resulting reaction mixture is acidified, and then the expected product is isolated.

5. A process according to one of claims 2 to 4, characterised in that the salt of pentanoic acid is the salt of sodium, potassium or a salt of tertiary amine.

6. A process according to one of claims 2 to 5, characterised in that the salt of pentanoic acid is produced extemporaneously from pentanoic acid and a base.

7. A process according to one of claims 2 to 6, characterised in that the salt of pentanoic acid is produced in situ from pentanoic acid and sodium carbonate.

8. A process according to one of claims 2 to 7, characterised in that the reaction mixture is acidified with sulfuric acid.

9. A process according to one of claims 2 to 8, characterised in that the expected compound (I) or its tautomeric form (II) is purified by recrystallisation in acetic acid.

10. The use of the compounds of claim 1 for the production of synthesis intermediates.

11. The use of the compounds of claim 1 for the production of 2-butyl-5-nitrobenzofuran-2-one.

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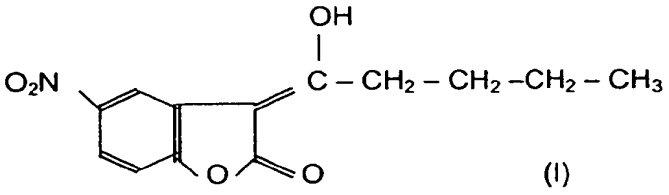

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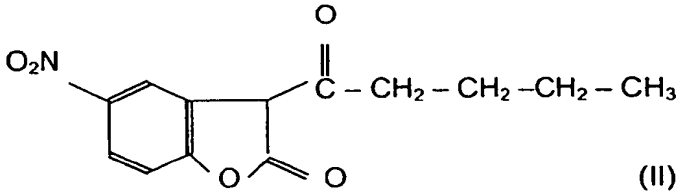

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which is 3-(1-hydroxy-pentylidene)-5-nitro-3H-benzofuran-2-one, a process for the preparation and use of the compound corresponding to formula (I) or its tautomeric form (II), a process for the preparation and use, particularly for the production of synthesis intermediates.

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EUROPEAN SEARCH REPORT

Application Number
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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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D,A	J.N. CHATTERJEA: JOURNAL OF THE INDIAN CHEMICAL SOCIETY, vol. 33, no. 3, 1956, pages 175-182, XP000946793 * page 177 * ---	1,2,10, 11	
D,A	J.N. CHATTERJEA: JOURNAL OF THE INDIAN CHEMICAL SOCIETY, vol. 34, no. 4, 1957, pages 299-305, XP000946792 * page 300 - page 301 * -----	1,2,10, 11	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31 August 2001	Paisdor, B

CATEGORY OF CITED DOCUMENTS

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